



Harvard Heart Letter

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HDL: The good, but complex, cholesterol

More HDL is better, but the benefits may depend on how you get there.

In the simplest telling of the cholesterol story, HDL (the so-called good cholesterol) fights LDL (bad cholesterol). Like knights in shining armor, HDL particles patrol the blood vessels, snatching cholesterol from circulating LDL particles and from the dangerous, gooey plaque that lines artery walls. The knights of the HDL carry their fatty cargo to the liver for recycling or disposal.

The *real* story isn't quite so simple. HDL is turning out to be a much more complex substance than we once believed. Instead of a single kind of particle, HDL is a family of different particles. Although they all contain lipids (fats), cholesterol, and proteins called apolipoproteins, some types are spherical while others are doughnut-shaped. Some types of HDL are great at plucking cholesterol from LDL and artery walls while other types are indifferent to cholesterol, and some even transfer cholesterol the wrong way—into LDL and cells.

To further complicate matters, different HDL types do more than just carry cholesterol. Some protect LDL from being chemically altered by oxygen, a change that makes LDL extra harmful to artery walls. Under some circumstances, though, they can do just the opposite. Various HDL particles can ease inflammation in artery walls, stimulate production of nitric oxide, a molecule that helps artery walls relax, and help prevent blood clots from forming inside arteries.

This diversity of function, and the equivocal evidence for the benefits of raising HDL, keep the spotlight on lowering LDL as part of the first line of defense in the fight

against heart disease. Even so, it is a good idea to try raising HDL when it is low. A low HDL is under 40 milligrams per deciliter of blood (mg/dL).

What causes low HDL?

There are many reasons why some people have low HDL and others have high HDL.

Genes certainly play a role by determining how much HDL your body makes and the proportion of different subtypes.

Lifestyle choices also affect HDL levels. Smoking, carrying too many pounds, and lack of physical activity tend to lower HDL. So does a diet high in refined carbohydrates (white bread,

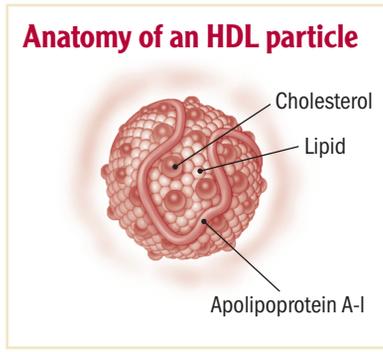
sugars, etc.). Medications such as beta blockers, anabolic steroids, progestins, and benzodiazepines can also depress HDL.

Poor ILLUMINATE-tion

Two kinds of medications have traditionally been used to raise HDL: niacin, which is also known as vitamin B₃, and fibrates, such as gemfibrozil (Lopid, generic) and fenofibrate (TriCor, generic).

Niacin increases HDL by an average of 7 mg/dL, and usually lowers LDL and triglycerides as well. Most people taking niacin experience flushing, an uncomfortable feeling of heat, itching, or tingling in the skin (see Ask the Doctor on page 8). Other side effects can include gastrointestinal, muscle, and liver problems.

Fibrates increase HDL about 4 mg/dL; they also lower total cholesterol, LDL, and triglycerides. The drawback is that one in three people experience an unwanted side



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HDL continued

effect, such as upset stomach, gas, diarrhea, or rash. Less common problems include liver and muscle damage.

In a number of trials over the past 40 years, the effect of these two medications translated into fewer heart attacks or strokes and longer survival. In a few trials, though, the drugs had little effect on cardiovascular disease. The equivocal results have some experts questioning whether the monetary and physical costs of taking niacin or a fibrate are worth the uncertain benefits.

A new drug called torcetrapib was specifically designed to raise HDL by blocking cholesteryl ester transfer protein (CETP), which is involved in the transfer of cholesterol between LDL and HDL. Yet in a major clinical trial called ILLUMINATE, reported in 2007, torcetrapib was a flop. Although it increased HDL by a whopping 60%, the volunteers who took torcetrapib didn't have any reduction in atherosclerosis compared with those taking a placebo. What they did have were small increases in blood pressure, as well as more cases of heart failure and procedures to open or bypass a blocked artery. The trial was stopped early on safety grounds, since volunteers taking a placebo were faring better than those taking torcetrapib.

The results torpedoed torcetrapib's chances of becoming a blockbuster drug, something its maker, Pfizer, was hoping for. They called into question the strategy of raising HDL by blocking CETP. And they also had some experts questioning across-the-board strategies for boosting HDL levels without paying close attention to the structure and function of the new HDL particles induced by the drug.

What to do

Current cholesterol guidelines focus on lowering elevated LDL first. Raising HDL comes later. That means a high HDL doesn't cancel out high LDL when it comes time to determine whether to start lifestyle or drug therapy. Instead, HDL takes a back seat to LDL.

That said, it is prudent to do what you can to boost your HDL, especially if it is under 40 mg/dL. Changes in lifestyle should be first on your list, since they do other wonderful things for the heart, bones, muscles, and psyche and have no harmful side effects. They include:

- **Exercising more.** Vigorous exercise is best for boosting HDL, but any extra exercise is better than none.
- **Losing weight.** If you are overweight, losing 5% to 10% of your current weight can raise HDL, along with reducing blood pressure and blood sugar.
- **Avoiding trans fats.** These artificial fats—found in hard margarines, many baked goods, and fried fast foods—lower HDL. Getting them out of your diet can improve both HDL and LDL levels.
- **Cutting back on refined carbohydrates.** Switching from refined carbohydrates to whole grains and adding more lean protein to your diet is a good dietary approach to increasing HDL.
- **Stopping smoking.** Quitting can improve HDL and do so much more for your heart and health.
- **Moderate alcohol intake.** Drinking alcohol in moderation (no more than one drink a day for women, one to two for men) raises HDL. If you don't drink, there's no need to start—exercise, losing weight, and other lifestyle changes are plenty.

Taking an LDL-lowering statin can also improve HDL, though you wouldn't start a statin for this purpose because the effect is small. If lifestyle changes don't do much, your doctor may suggest that you take niacin or a fibrate. Results from ongoing trials of a prescription form of intermediate-release niacin (Niaspan) suggest that combining it with a statin is a safe and effective way to improve cholesterol levels and fight atherosclerosis.

Ongoing efforts to increase the body's production of atherosclerosis-fighting HDL and tinker with the alphabet soup of helper molecules, like CETP, ABCG1, LCAT, PLTP, and SR-B1, may someday lead to new ways to deal with low HDL. In the meantime, the old standbys are good options. ♥

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